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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/658,699	09/09/2003	Christopher M. Starr	30610/30013A	2307

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/658,699	STARR, CHRISTOPHER M.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-37,40 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-37 and 40-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a divisional of 09/562,427, now abandoned.

The amendment filed on June 15, 2005, amending claims 33-36 and 41 and canceling claims 38-39, has been entered.

Claims 33-37 and 40-41 are pending and are under consideration.

Response to Arguments

Applicant's amendment and arguments filed on June 15, 2005, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-37 and 40-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 33-37 are drawn to a pharmaceutical composition comprising a human N-acetylgalactosamine-4-sulfatase (ASB). Claims 40-41 are drawn to a pharmaceutical composition comprising human ASB. The claims encompass recombinants, variants and mutants of human ASB and any ASB. Therefore, the claims are drawn to a genus of polypeptides having any structure. The specification only teaches one species, a human ASB of 533 amino acids with a signal peptide of 41 amino acids (specification, page 11 and Peters et al. – form PTO-1449). One species is not enough to describe the whole genus and there is no evidence on the record of the relationship between the structure of this species and the structure of any recombinants, variants and mutants of any ASB. The specification also does not describe which residues of ASB are needed to impart a variant or mutant with ASB activity. Therefore, the specification fails to describe a representative species of the genus comprising variants and mutants of any ASB.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 33-37 and 40-41.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that the usage of "N-acetylgalactosamine-4-sulfatase"in the specification and original claims makes clear that this term is different from the terms "biologically active fragment, mutant or analog thereof". Examiner respectfully disagrees. The claims are given their broadest reasonable interpretation (see MPEP 2111). A human N-acetylgalactosamine-4-sulfatases encompass a genus of any or all

human N-acetylgalactosamine-4-sulfatase, including their fragments, recombinants, variants and mutants. Therefore, the genus comprising any or all recombinants, variants and mutants of any human N-acetylgalactosamine-4-sulfatase does not possess any common attributes other than having N-acetylgalactosamine-4-sulfatase activity. Therefore, the specification lacks description of a representative number of species to describe the whole genus. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

Claims 33-37 and 40-41 are rejected under 35 U.S.C.. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising human ASB taught by Peters et al., does not reasonably provide enablement for pharmaceutical compositions comprising any ASB. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 33-37 are drawn to a pharmaceutical composition comprising human N-acetylgalactosamine-4-sulfatase (ASB). Claims 40-41 are drawn to a pharmaceutical composition comprising human ASB. The claims encompass recombinants, variants and mutants of human ASB and any ASB. Therefore, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of ASB broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which

amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the amino acid sequence of only one ASB. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. The specification provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any human ASB because the

specification does not establish: (A) regions of the protein structure which may be modified without affecting ASB activity; (B) the general tolerance of ASB to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including recombinants, variants and mutants of any human ASB. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of human ASB having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that the usage of "N-acetylgalactosamine-4-sulfatase"in the specification and original claims makes clear that this term is different from the terms "biologically active fragment, mutant or analog thereof". Examiner respectfully disagrees. The claims are given their broadest reasonable interpretation (see MPEP 2111). A human N-acetylgalactosamine-4-sulfatases encompass a genus of any or all human N-acetylgalactosamine-4-sulfatase, including their fragments, recombinants,

variants and mutants. Therefore, the claims comprise any or all recombinants, variants and mutants of any human N-acetylgalactosamine-4-sulfatase does not possess any common attributes other than having N-acetylgalactosamine-4-sulfatase activity. As discussed above, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a specific knowledge of and guidance with regard to which specific amino acids in the protein's sequence, can be modified such that the modified polypeptide continues to have said claimed activity. It is this specific guidance that applicants do not provide. Without specific guidance, those skilled in the art will be subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation. While the art may teach in general the structure of N-acetylgalactosamine-4-sulfatase, conserved amino acid sequences, and etc, such teachings will not reduce the burden of undue experimentation on those of ordinary skill in the art.

Hence the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33-37 and 40-41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Crawly et al. and Mundorf et al. and Bam et al.

Claims 33-37 are drawn to a pharmaceutical composition comprising a human recombinant N-acetylgalactosamine-4-sulfatase (ASB), polyoxyethylenesorbitan 20 or 80, and a carrier. Claims 40-41 are drawn to a pharmaceutical composition comprising a human N-acetylgalactosamine-4-sulfatase (ASB), polyoxyethylenesorbitan 20 or 80, and a carrier, wherein the composition has the properties recited in claim 40 and are produced by the purification steps recited in claim 41.

Crawley et al. (form PTO-1449 – Reference C6) teaches a pharmaceutical composition comprising a human N-acetylgalactosamine-4-sulfatase (ASB) and a carrier (page 1865). The composition of Crawley et al. possesses the properties recited

in claim 40 since the composition of Crawley and the instant invention contains the ASB of Peters et al. (page 1865). The protein of Crawley et al. was produced by the same purification process as recited in claim 41 (page 1865). However, Examiner notes that patentability of a product does not depend on the method used in producing the product (MPEP 2113).

The difference between the composition of Crawley and the instant invention is that the composition of Crawely et al. does not contain polyethylenesorbitan 20 or polyethylenesorbitan 20 (also known as polysorbate or tween).

Mundorf et al. (form PTO-892 – U.S. Patent No. 5,266,310) teaches that polysorbate 20 are stabilizing agents used in pharmaceutical compositions (Column 3). Mundorf et al. also teaches that the concentration of the polysorbates can be varied depending on the carrier used (Column 3). Bam et al. (form PTO-892) teaches that polysorbate 80 are stabilizing agents used in pharmaceutical compositions (page 258).

Combining the teachings of Crawley et al., Mundorf et al. and Bam et al., it would have been obvious to one having ordinary skill in the art use polysorbate 20 or polysorbate 80 in making the composition of Crawley et al. in order to prolong its shelf life. One of ordinary skill in the art would have been motivated to use polysorbate 20 or polysorbate 80 since Mundorf et al. and Bam et al. teach that polysorbates stabilize proteins in pharmaceutical compositions and prolong its shelf life. One of ordinary skill in the art would have had a reasonable expectation of success since Mundorf et al. and Bam et al. teach the use of polysorbate 20 or polysorbate 80 as stabilizing agents in

pharmaceutical compositions and Crawley et al. successfully teaches pharmaceutical compositions comprising ASB and a carrier.

Therefore, the above references render claims 33-37 and 40-41 prima facie obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the human ASB of Crawley does not possess the properties of the composition claimed in claim 40 because the ASB of Crawley exhibits two distinct bands on SDS PAGE, comprise 70% precursor protein and has a specific activity of 25-30 mUnits/mg. Examiner respectfully disagrees. Claim 40 recites that the ASB has one major band between about 65-70kDa. The ASB of Crawley has a band at 66kDa, which represents the precursor that makes up 70%. Therefore, said band can be construed as the major band. The ASB of Crawley has a mean specific activity of 29,930 ± 7,250 mUnits/mg using 4-methylumbelliferyl sulfate as the substrate. Thereofore, the ASB of Crawley has a specific activity of 37,180 mUnits/mg which can be construed as "about" 40,000 mUnits/mg. Further, claim 40 (j) recites that ASB has "greater than about 95% purity by RP-HPLC". The ASB of Crawley would have greater than about 95% purity when prepared using RP-HPLC.

Applicants also argue that Crawley does not disclose the method by which the ASB was purfied and therefore Crawley does not anticipate claim 41. Examiner respectfully disagrees. The instant rejection is an obvious rejection under 35 U.S.C.

103 and not an anticipation rejection. And more importantly, patentability of a product does not depend on the method used in producing the product (MPEP 2113).

Applicants also argue that there is no motivation to combined the cited references because both Bam and Mundorf teach using polysorbates for making topical solution. Examiner respectfully disagrees. The claims do not limit the composition to a topical solution, but any pharmaceutical composition. Contrary to Applicants' argument, there is motivation to combine the references. Since Bam and Mundorf teach that polysorbates are used to stabilize proteins and thus prolong their shelf life, one having ordinary skill in the art would have been motivated to use polysorbate 20 or polysorbate 80 to stabilize the ASB of Crawley and prolong its shelf life.

Applicants also argue that there is no reasonable expectation of success in making a successful pharmaceutical composition using polysorbate as the stabilizing agent because not all proteins are stable in polysorbate solution. Examiner respectfully disagrees. MPEP 2143.02 teaches that Obviousness does not require absolute predictability, but only a reasonable expectation of success. As applicants have argue, polysorbates do not stabilize certain proteins. However, as Bam and Mundorf teaches, polysorbates have been widely used to stabilize many different classes of proteins. An ordinary person skilled in the art would have expected a reasonable level of success in making a pharmaceutical composition as claimed since Bam and Mundorf teach how to make compositions using polysorbates. Further, the claims are simply drawn to a pharmaceutical composition comprising a human ASB, carrier and polysorbate and do not recite a limitation that the ASB be stabilized by polysorbate.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 33-37 and 40-41 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of copending Application No. 10/290,908. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are claiming common subject matter, as follows: Claims 33-36 and 38-39 of the instant application and claims 1-16 of 10/290,908 are both directed to a pharmaceutical compositions comprising ASB and polysorbate 20 or polysorbate 80 (the ASB of the instant application and the referenced application is identical).

The concentration of polysorbates and characteristics of the ASB and method used to produce ASB claimed in claims 37 and 40-41 are specific embodiments of the pharmaceutical composition described in the reference application. The specification of the reference application supports the recited enzyme in the pharmaceutical

composition and the specific concentration of polysorbate 20 or polysorbate 80, characteristics of the ASB and methods of producing the ASB protein (pages 5-12) that would anticipate the pharmaceutical composition of claims 37 and 40-41 of the instant application. Claims 33-41 of the instant application cannot be considered patentably distinct over claims 1-16 of the reference application when there is specifically recited embodiment that would anticipate mainly claims 37 and 40-41 of the instant application. Alternatively, claims 37 and 40-41 of the instant application cannot be considered patentably distinct over claims 1-16 of the reference application because it would have been obvious to one having ordinary skill in the art to modify claims 1-16 of the reference by selecting a specifically disclosed embodiment that supports those claims, i.e. active enzyme and concentration of polysorbates used, methods of purifying ASB, etc. One of ordinary skill in the art would have been motivated to do this because the embodiments claimed in the instant claims are disclosed as being a preferred embodiment within claims 1-16 of the reference application. Therefore, the conflicting claims are not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In response to the previous Office Action, applicants have stated that upon allowance of 10/290,908, a terminal disclaimer will be filed. Therefore, the rejection has been maintained.

None of the claims are in condition for allowance.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652

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